



Principles of transfusion medicine in small animals

Anne Lanevski, K. Jane Wardrop

Abstract — The purpose of this review was to provide the reader with an updated overview of small animal transfusion medicine, and an approach to integrating it into private practice, based on a review of the veterinary and human literature spanning the last 3 decades. Electronic, online databases that were searched included CAB International and Medline; multiple keywords or subject headings were searched that were appropriate to each of the sections reviewed: canine and feline blood groups, blood-typing and crossmatching, donors, blood collection, storage, blood components, blood transfusion, blood component therapy, blood substitutes, and adverse reactions. The safe use of blood component therapy requires knowledge of blood groups and antibody prevalence, and knowledge of the means to minimize the risk of adverse reactions by including the use of proper donors and screening assays that facilitate detection of serological incompatibility. The 2 assays available to the practitioner are crossmatching, which is readily done in-house, and blood typing. Blood typing is available in the form of a commercial testing kit, through use of purchased reagents, or via a request to an external laboratory. The risk of potentially fatal adverse reactions is higher in cats than in dogs. The decision to transfuse and the type of product to administer depend on several factors, such as the type of anemia and the size of the animal. In conclusion, transfusion medicine has become more feasible in small animal practice, with improved access to blood products through either on-site donors, the purchase of blood bank products, external donor programs, or the availability of blood component substitutes.

Résumé — **Principes de la médecine de transfusion chez les petits animaux.** Le but de cette revue était de fournir aux lecteurs une vue d'ensemble à jour de la médecine de transfusion chez les petits animaux et une approche d'intégration en pratique privée basée sur une revue de la littérature tant vétérinaire qu'humaine s'étendant sur trois décennies. Les bases de données informatiques retenues comprennent CAB International et Medline; les mots-clés multiples ou les rubriques appropriées à chaque section analysée ont été recherchés : groupes sanguins canins et félins, groupes sanguins et compatibilité croisée, donneurs, prélèvements, entreposage, composantes du sang, transfusion sanguine, thérapie par composantes du sang, substituts du sang et réactions indésirables. L'utilisation sécuritaire des thérapies par composantes du sang requiert la connaissance des groupes sanguins et de la prévalence des anticorps ainsi que les moyens pour minimiser les risques de réactions indésirables dont le choix des bons donneurs et les tests de dépistage permettant la détection de l'incompatibilité sérologique. Les deux analyses disponibles pour le praticien sont la compatibilité croisée, facilement réalisable sur place, et la détermination des groupes sanguins. La détermination des groupes sanguins peut se faire par utilisation d'une trousse comprenant des réactifs disponibles dans le commerce ou par un laboratoire spécialisé. Les risques de réactions indésirables mortelles sont plus élevés chez les chats que chez les chiens. La décision de transfuser et le type de produit à administrer dépend de nombreux facteurs tels que le type d'anémie et la grosseur de l'animal. En conclusion, la médecine de transfusion est maintenant plus accessible en pratique des petits animaux à cause d'une meilleure disponibilité des produits sanguins reliée à la présence de donneurs sur place, à l'achat de produit provenant de banques de sang, à l'accès à des donneurs externes ou à la disponibilité de substituts aux composantes du sang.

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Département de pathologie et microbiologie, Faculté de médecine vétérinaire, Université de Montréal, 3200, Sicotte, C.P. 5000, Saint-Hyacinthe, Québec J2S 7C6 (Lanevski); Clinical Pathology Laboratory, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Washington State University, Pullman, Washington 99164-6610 USA (Wardrop).

Address correspondence and reprint requests to Dr. Anne Lanevski.

Introduction

The purpose of this review is to provide the reader with an updated overview of small animal transfusion medicine, and an approach to integrating it into private practice, based on a review of the recent veterinary and human literature. Transfusion medicine has gradually become more feasible in small animal practice, with improved access to blood products through either on-site donors, the purchase of blood bank products, external donor programs, or the availability of blood component substitutes. However, the safe use of blood component therapy requires knowledge of blood groups and antibody prevalence, and knowledge of the means to minimize the risk of adverse reactions by including the use of proper donors and screening assays that facilitate detection of serological incompatibility. This review covers a brief history of transfusion medicine, an update on canine and feline blood groups and known blood incompatibilities, laboratory testing for blood type or compatibility, donor selection and blood collection, storage of blood components, blood component and blood substitute therapy, and adverse reactions in small animal transfusion medicine.

Literature search

The veterinary literature was emphasized, and the human literature was cited to provide support for specific concepts and guidelines in veterinary transfusion medicine for those areas in which extensive veterinary research has not yet been performed. The 2 main, electronic, online databases used were CAB International (Commonwealth Agricultural Bureaux International, Wallingford, Oxon, UK) (1973–2000), for the veterinary literature, and Medline (National Library of Medicine, Bethesda, Maryland, USA) (1966–2000), for the human literature. Multiple keywords or subject headings were searched appropriate to each of the sections reviewed: canine and feline blood groups, bloodtyping and cross-matching, donors, blood collection, storage, blood components, blood transfusion, blood component therapy, blood substitutes, adverse reactions. Search terms or subject headings included transfusion medicine, history, canine, feline, blood groups, alloantibodies, cross-matching, bloodtyping, diagnosis, donors, adverse effects, therapeutic use, plasma, coagulation factors, toxicity, incompatibility, blood components, platelets, storage, blood substitutes, and thrombocytopenic purpura.

History

The history of transfusion medicine dates back to the Early Modern Period immediately following the Renaissance, with landmark discoveries, such as William Harvey's theory of circulation (1628), making advances in this field possible. It was not until the 19th century that transfusion became a more common occurrence, albeit as a high-risk procedure, in women suffering from post-partum hemorrhage. The 20th century saw several major breakthroughs that made this practice safer and more widespread, including the discovery of anticoagulants and preservatives for blood products, the description of human blood groups, and the development of compati-

bility assays (1). The tragic occurrence of World War II enhanced developments in transfusion medicine, including large-scale blood-banking under the Red Cross. In the veterinary field, transfusion medicine emerged as a practice from the 1950s onwards (2). Recently, research on substitutes for oxygen transport led to the approval in 1998 by the United States Food and Drug Administration of a hemoglobin-based oxygen carrying solution for use in dogs.

Blood groups

Erythrocytes possess particular antigens (glycoproteins or glycolipids) on the surface of their cell membranes that allow their classification into blood groups. A characteristic of these antigens is their ability to trigger a reaction caused by circulating anti-erythrocyte antibodies in the opponent host or donor. These antibodies may occur naturally or be induced following a previous transfusion. A severe, and potentially life-threatening, situation is one in which the interaction leads to the destruction by hemolysis of red blood cells (RBCs). In type B cats receiving type A blood, the rapid destruction of RBCs may be mediated by IgM and complement fixation, as well as the release of potent vasoactive compounds. This may cause shock and generally occurs when the patient possesses antibodies towards the transfused RBCs. In other instances, the antibody-red cell antigen interaction is less severe, and the most important outcome is that the transfusion loses its efficacy as the mean survival time of transfused RBCs is drastically reduced.

Canine blood groups — The terminology for canine blood groups has changed over time. Currently, the prefix DEA ("dog erythrocyte antigen") is used, and antigens from 5 blood groups can be characterized by using commercial antisera. The most important blood groups are DEA-1 (1.1 and 1.2) and DEA-7. The DEA-1 group has 4 alleles. A dog may be DEA-1-negative, or DEA-1.1- or DEA-1.2-positive. Recently, DEA-1.3 has been described (3). Transfusion of DEA-1.1 type erythrocytes in a DEA-1-negative recipient results in the formation of anti-DEA-1.1 alloantibodies, and as a result, the lifespan of the transfused RBCs is decreased (4). More importantly, subsequent transfusions in the same patient and with the same blood type will result in an acute hemolytic crisis. Similar to DEA-1.1 incompatibility, transfusion of DEA-1.2 type erythrocytes in a DEA-1-negative recipient that possesses circulating anti-DEA-1.2 alloantibodies results in a half-life of transfused erythrocytes of 0.5 d (5). In contrast, DEA-7 is a soluble, nonerythroid antigen that adsorbs to the red cell surface. Dogs that are DEA-7 negative may possess naturally occurring anti-DEA-7 alloantibodies, but their importance is debated (4,6,7). For these reasons, ideal canine donors should at least be DEA-1.1 and -1.2 negative. In screening for candidate donors, DEA-1.1-negative dogs should be further tested for DEA-1.2. Other canine blood groups are infrequent, and incompatible transfusions with these blood groups do not generally result in a clinically apparent transfusion reaction, although the lifespan of transfused RBCs may be diminished (8,9).

Table 1. Crossmatching assay procedure

1. Centrifuge (1000 × g or 3400 rpm) whole blood from a red-top (no anticoagulant) tube (Vacutainer; Becton-Dickinson, Franklin Lakes, New Jersey, USA) in order to obtain serum, and whole blood from a purple-top (EDTA) tube (Vacutainer; Becton-Dickinson) in order to obtain RBCs from both the patient and donor.
2. Washing RBCs: resuspend 0.25 mL of RBCs in 2 to 4 mL of saline; centrifuge 1 min, remove supernatant, and repeat the procedure twice; remove supernatant.
3. Resuspend 0.1 to 0.2 mL of RBCs in approximately 4.8 mL saline in order to obtain a 2% to 4% RBC solution.
4. In 3 tubes identified "Major," "Minor," and "Control" add the following:

	"Major" crossmatch	"Minor" crossmatch	Control
Patient	2 drops serum	1 drop RBC solution*	1 drop patient RBC solution* + 2 drops patient serum
Donor	1 drop RBC solution*	2 drops serum	1 drop donor RBC solution* + 2 drops donor serum
5. Incubate tubes 15 min at 37°C.
6. Centrifuge tubes 15 s.
7. Reading results: Note serum color and record any hemolysis. Then gently resuspend the red cell button into the overlying serum layer, noting the presence of agglutinating clumps. Next, place a drop of resuspended RBCs on a slide, apply coverslip, and read at 100X and 400X. If the crossmatch is compatible, the RBCs should be individually distributed. Hemolysis (compared to control) or agglutination is seen with an incompatible crossmatch.
8. Rouleaux, a physiological plasma-related phenomenon, may sometimes be observed. In order to distinguish this from agglutination, centrifuge the tubes again for 15 s, remove serum, and add 2 drops of saline; then centrifuge the tubes once more and reexamine the RBC suspensions.

* — saline solution containing 2 to 4% RBCs; EDTA — ethylenediaminetetraacetic acid

Feline blood groups — Cats have an AB blood group system, and their RBCs may be A, B, or, rarely, AB. A and B are alleles in the same locus, where A is dominant over B. The mode of inheritance for AB has not yet been described (10).

The frequency of feline blood types varies according to breed and geographic location, but most cats (> 95%) have type A RBCs. Less than 5% of the cat population possesses the type B RBCs, and 1% or less of domestic shorthair or longhair cats have type B blood. The frequency of type B blood is higher in certain breeds and may be as high as 77% in the British shorthair (11–13). Most type B cats have powerful naturally occurring anti-A alloantibodies, such that transfusion of type A blood into a type B cat will result in an acute hemolytic reaction. The half-life of transfused RBCs following such transfusions is approximately 1 h. Approximately 30% of type A cats will possess weakly agglutinating anti-B antibodies, such that only a minor reaction occurs when a type A cat is transfused with type B blood, rendering the transfusion inefficient. The half-life of the transfused RBCs in these transfusions is approximately 2 d (14). Type AB cats do not possess anti-A or anti-B antibodies and can be safely transfused with type A blood (15). Although a type AB cat could technically receive RBCs from a type A or type B cat, anti-A alloantibodies in plasma from a type B cat could cause a reaction. Ideally, 2 types of feline donors are desired: a type A cat, at the very least, and an available type B cat, whenever possible.

Laboratory testing: blood-typing and crossmatching

Blood typing enables the practitioner to identify the blood group of the patient or a candidate donor. This assay is based on a hemolytic or agglutinating reaction in which the reagent or antibody reacts with the RBCs of the test subject. The crossmatching test does not identify the blood group but, instead, detects serological incompatibility between a candidate donor and the patient. Reasons for testing, using either of these methods, prior to transfusion include the need to avoid an acute hemolytic reaction during or following transfusion, an assurance of an optimal lifespan of the transfused RBCs, the prevention of incompatible blood transfusions in the future, and the prevention of neonatal isoerythrolysis.

Blood-typing cards are available commercially for the cat and the dog (Rapid Vet-H feline and canine blood-typing cards; DMS Laboratories, Flemington, New Jersey, USA). The test is simple and quick to perform; it involves the mixing of a drop of blood from the animal to be tested with a drop of the antibody reagent and then noting the presence of agglutination. For the dog, the reagent is a murine monoclonal anti-DEA-1.1 antibody; for the cat, the reagents are an anti-B reagent (a wheat germ lectin) and natural anti-A antibody (16). Controls may be included with the cards. However, care should be taken to ensure that these controls contain stable cells and that hemolysis of the controls has not occurred. False positive reactions have been reported with commercially

available DEA-1.1 typing cards (17). An alternative for blood typing in dogs is to submit samples to an external laboratory. Blood typing in dogs is particularly indicated for screening candidate donors and for emergency situations in which there can be no delay in waiting for a result from an external laboratory. It should be noted that the possibility of false positive reactions by using the DEA-1.1 typing cards could lead to inadvertent transfusion of DEA-1.1-positive blood to a DEA-1.1-negative recipient that falsely tested DEA-1.1-positive. This animal will be sensitized and react to subsequent transfusions with DEA 1.1-positive blood. For this reason, it is preferable to test donors rather than recipients. For cat blood typing, in-house typing other than with the commercially available typing cards is feasible, if both type A and type B cat donors are available. Heat-inactivated serum from the type B cat can be used as anti-A reagent; for detection of type B blood, a wheat germ lectin (*Triticum vulgare*) solution can be used (*Triticum vulgare* lectin, 2-mg vial [product no. L9640; Sigma Chemical Company, St. Louis, Missouri, USA], reconstituted with 20 mL of phosphate-buffered saline for a 100- μ g/mL solution, stored at 4°C) (14). Blood from donors of known blood type can serve as a control for the assay.

Crossmatching requires that centrifuged RBCs from the donor or recipient be washed several times with saline and prepared as a 2% to 4% suspension before being incubated at 37°C with serum from the recipient or donor, respectively (Table 1). The only pieces of equipment required are a centrifuge and a temperature-regulated hot water bath or incubator.

Screening tests to detect serologic incompatibility are strongly recommended in dogs, even in the event of a first transfusion where the risk of a serious adverse reaction is low. Testing becomes essential if the animal has already received a transfusion, especially if the donor is not known to be DEA-1.1 or DEA-1.2-negative (4). The risk of blood incompatibility is much higher in the cat, especially in purebred cats (except for Siamese) in which the frequency of B-cats is higher. Blood typing or crossmatching is essential to minimize this risk, although the risk is lower in shorthairs. It is important to note that a negative result from crossmatching blood from a donor and a patient does not mean that 2 subjects have the same blood type. Also, crossmatching does not provide a guarantee of leukocyte, protein, or platelet compatibility, and, in some cases, it may be too insensitive to detect anti-erythrocyte antibodies (18).

Donor selection and blood collection

Several approaches are available in order to obtain blood products. One approach is to purchase products as the need arises from a blood bank. There are several drawbacks with this option, such as delays in obtaining blood components, limitations as to the availability of certain blood components when requested, and blood components that are not produced by a given blood bank. Another approach is to have access to donors either as in-house donors or from an external donor program. There are advantages and disadvantages to both options, and the choice should take into account the practice's needs (Table 2) (19–21). For an

Table 2. Advantages and disadvantages of in-house donors versus an external donor program

In-house donors	
Advantage	• donor is readily available
Disadvantage	• higher maintenance cost • a donor may not fulfill the practice's need for blood products
External donor program	
Advantage	• less costly • multiple donors provide a greater supply of blood product • collection may be scheduled at a convenient time • sensitizes owner to the value of veterinary medicine in society
Disadvantage	• requires advance planning • requires storage of blood products

external donor program, a list of reliable donors has to be established. As the list grows, the blood collection interval can be increased. However, too many donors increase yearly health screening costs. With either on-site or external donors, a donor log should be kept in addition to the donor's medical file. The log can contain the name, blood type, scheduled dates for yearly or twice yearly screening tests, blood collection dates, and the owner's contact information, if it is an external donor. A transfusion log should also be kept with information on each transfusion, including the date of transfusion, donor, type and volume of blood component used, recipient, diagnosis, and problems encountered, such as adverse reactions. In addition, a note that the recipient has received a blood transfusion should be included in a visible location in the recipient's medical file (20).

The ideal canine donor should have the following characteristics: weigh more than 30 kg, have taut neck skin that permits easy access to the jugular vein, have a packed cell volume that is at least 0.40 L/L, have demonstrated a good temperament and be in fit physical condition, have no previous history of transfusion or pregnancy, be DEA-1.1 and DEA-1.2-negative, and possess adequate levels of von Willebrand factor (vWF).

The ideal feline donor should have the following characteristics: weigh more than 4.5 kg, have a packed cell volume that is at least 0.35 L/L, have demonstrated a good temperament, and be in fit physical condition.

Proper maintenance of donors requires up-to-date vaccinations; fecal floatation every 6 mo if there is contact with new animals; a yearly hemogram, clinical chemistry profile, and screen for infectious diseases; and, in the dog, preventative heartworm therapy in regions where it is appropriate. At each blood collection, the donor's weight, temperature, and packed cell volume should be checked (22–24).

Blood collection usually should not exceed 15–20 mL/kg bodyweight (BW) every 3 wk in dogs, and 10–15 mL/kg BW or a total of 60 mL every 3 wk in cats. This schedule may require iron supplementation. An increased interval is recommended, if the packed cell volume or plasma protein drops significantly after blood collection (20,24).

Anticoagulants and preservatives

Heparin and citrate are anticoagulants that will not contribute to cell preservation during long-term storage and whole blood collected in these anticoagulants should be used within 24 h. Commonly used preservatives include acid citrate dextrose (ACD), citrate phosphate dextrose (CPD and CP2D), and citrate-phosphate-dextrose-adenine (CPDA-1), in which the added dextrose, phosphate, and adenine favor the viability of RBCs, permitting their storage for up to 3 to 5 wk, depending on the preservative (25–27). Additive solutions (Adsol, Fenwal Division of Baxter Healthcare Corporation, Deerfield, Illinois, USA; Nutricel, Cutter Biological, Division of Miles Laboratories, Emeryville, California, USA; Optisol, Terumo Medical Corporation, Somerset, New Jersey, USA) can be added to blood from which plasma has been removed. These solutions contain factors, such as dextrose, adenine, mannitol, and the sodium chloride, needed by RBCs to maintain their energy metabolism and viability during storage. Whole blood may be collected using ACD, CPD or CPDA-1. For dogs, a standard 450 mL CPDA-1 bag enables the collection of one unit of blood. If sedation is required, it is best to avoid acepromazine, as it may alter platelet function. Butorphanol (0.1 mg/kg BW, IV), administered 10–15 min before collection, has been recommended in the dog (28). In the cat, ketamine may be used as needed: 2 to 4 mg/kg BW, IV, plus 0.1 to 0.2 mg/kg BW diazepam, IV, works well. In the cat, blood can be collected via jugular vein venipuncture into a syringe containing either ACD, CPD, or CPDA-1 (1 mL/9 mL of blood), or heparin (5 units/mL of blood) by using a 19- to 20-gauge needle or butterfly. It can be stored in a small blood bag, as long as a preservative solution is used (29).

Blood product indications

The choice of blood components to be used cannot be based solely on the packed cell volume; the rate, as well as the quantity and type of components lost or missing, influences the clinician's choice. Whole blood is indicated in a patient that requires several blood components or has acutely lost more than 50% of its total blood volume, in order to replace both oxygen-carrying capacity and oncotic activity. For example, fresh whole blood containing labile coagulation factors would be indicated in a patient suffering from hemorrhage due to thrombocytopenia, hemophilia, liver insufficiency, or disseminated intravascular coagulation (DIC), whereas whole blood containing stable coagulation factors would be indicated in vitamin K antagonist rodenticide toxicosis (30). The calculation of a patient's total blood volume is 85–90 mL/kg BW in the dog and 65–75 mL/kg BW in the cat (31). Whole blood administration attains 2 goals: expansion of the blood volume and tissue reoxygenation. Platelets gradually lose their viability following refrigeration, such that they will not contribute significant procoagulant activity when previously refrigerated whole blood is used (32,33). However, whole blood collected within the previous 24 h still contains much of its labile coagulation factor activity (factors V and VIII), as well as its stable coagulation factor activity. After this time, its labile coagulation factor activity is gradually lost

(34–36). Whole blood is not the ideal product where tissue reoxygenation is specifically required and there is little or no need for plasma volume expansion. Examples of this are acute hemorrhage with less than 50% of total blood volume loss, in which the volume expansion needed may be provided by crystalloid solutions and tissue reoxygenation can be supplied by packed RBCs. Other examples include chronic hemorrhage, hemolytic anemia, or nonregenerative anemia. Packed red cell transfusion is preferable to whole blood transfusion in these situations, since whole blood transfusion can lead to hypervolemia in these patients (34). An exception is with the treatment of small dogs or cats, where it may be more difficult to prepare small volumes of packed RBCs.

Packed RBCs are prepared by removing 200 to 250 mL of plasma from 450 mL (1 unit) of whole blood after centrifugation. The packed cell volume of the RBC preparation is approximately 0.70 to 0.80 L/L, and the RBCs can be resuspended in a protein-poor additive solution, such as Adsol, to a packed cell volume of 0.55 to 0.65 L/L. Shelf life depends on the preservative solution used (37–39). The transfusion of packed RBCs is indicated for tissue reoxygenation and is ideal for a normovolemic, anemic patient.

Plasma contains 2 labile coagulation factors: V and VIII. If freshly collected human plasma is not frozen, half of the procoagulant activity associated with factor VIII (but not factor V) is lost within the first 24 h, whereas other coagulation factors remain stable (40). Fresh frozen plasma (FFP) is plasma that has been separated from RBCs and frozen at -18°C within 8 h of collection (if preserved with CPDA-1, CPD, or CP2D; 6 h if preserved with sodium citrate or ACD); plasma frozen after this period is referred to as frozen plasma (FP). One unit of FFP has an approximate volume of 200 to 250 mL and contains labile and stable coagulation factors. The main indications for FFP administration are a lack of coagulation factors associated with hepatic insufficiency, DIC, vitamin K deficiency (rodenticide toxicosis, liver insufficiency, biliary tract obstruction, malabsorption syndrome, chronic antibiotic use), a need for plasma volume expansion, or a massive blood loss within a few hours. Other indications include a congenital or a hereditary deficiency in coagulation factors, such as hemophilia A, B, or von Willebrand's disease. On the other hand, FP, which lacks labile coagulation factor activity, may be used to treat conditions in which stable coagulation factors are needed, such as rodenticide toxicosis or hemophilia B. As much as possible, FFP should be reserved for patients requiring labile coagulation factors (DIC, hemophilia A, and von Willebrand's disease), and FP used for other disorders. Plasma (FP or FFP) is not indicated as a long-term source of protein for patients suffering excessive protein loss (enteropathy, nephropathy, exudative dermatitis) or suffering from inadequate intake, but it may be used initially in the emergency management of such patients (41,42). Enteral or parenteral nutritional support may be more effective in patients suffering protein loss, as it may favor hepatic albumin synthesis. An instance in which plasma is indicated for hypoproteinemia due to protein loss is acute albumin loss, such as occurs in burn victims (43).

Special clinical considerations for transfusion of whole blood or packed RBCs

Choosing the proper blood component or components and calculating the amount to administer to the patient must be based on a case-by-case evaluation. In acute hemorrhage, packed cell volume may be a poor indicator of the degree of blood loss. Since all blood components are lost in hemorrhage, signs of shock may be seen initially when the packed cell volume is within reference limits. The packed cell volume in such patients will gradually drop over the 72 h following the initiating incident, as extravascular fluid is redistributed and enters the intravascular space, assuming that there has been no volume replacement with crystalloids, in which case the packed cell volume will drop more quickly. The potential for survival depends mainly on 2 factors: reestablishment of the blood volume and tissue reoxygenation. Initial fluid therapy with crystalloids or colloids is essential to reestablish blood volume. This will be sufficient for losses that do not exceed 20% of the patient's total blood volume. For losses exceeding 20%, whole blood or packed red cell transfusion is indicated. Losses between 20% and 50% of blood volume require crystalloids and packed RBCs (44). Whole blood is unnecessary, as there is no need for colloids, coagulation proteins, or platelets. Losses between 50% and 100% of total blood volume require replacement of RBCs and a correction of colloidal oncotic pressure. In such an instance, whole blood or, alternatively, packed RBCs combined with either plasma or an equivalent product (dextran-70, pentastarch, or hetastarch) that will favor blood volume expansion should be administered; whole blood is not essential, as there is no need for coagulation proteins or platelets. Losses exceeding 100% of total blood volume (trauma) require a replacement of all blood components; therefore, whole blood transfusion is necessary. Hemostasis imbalance (hemophilia, von Willebrand's disease, rodenticide toxicosis, liver insufficiency, DIC, thrombocytopenia) may require multiple blood components or fresh whole blood (45).

Patients that suffer from nonregenerative anemia are normovolemic and may develop pulmonary edema due to hypervolemia following whole blood transfusion. For these patients, packed RBC transfusion is the treatment of choice.

Among other blood components that may occasionally be indicated, cryoprecipitate and platelet-rich plasma are worthy of mention. Cryoprecipitate is rich in vWF, factors VIII, XIII, fibrinogen, and fibronectin. It is especially useful in vWF-deficient patients either suffering from blood loss or for whom surgery (such as elective orthopedic surgery) is anticipated. The advantage of cryoprecipitate is that it enables the replacement of one or several coagulation proteins with the administration of a small volume of plasma. Cryoprecipitate is obtained by slowly thawing fresh frozen plasma at 4°C until some crystals remain in suspension. After this gradual thaw, the bag is centrifuged and the supernatant is removed. Cryoprecipitate thus obtained can be frozen at -18°C for up to 1 y. Other indications for using cryoprecipitate are bleeding hemophilia A patients, or patients suffering hypo- or dysfibrinogenemia (46,47).

The use of platelet-rich plasma is occasionally indicated in veterinary practice. The main limitations with platelet-rich plasma therapy are threefold: the difficulty in obtaining a sufficient volume of platelet-rich plasma to be of therapeutic value in a patient; the short platelet lifespan requiring the use of platelet-rich plasma as soon as possible after its preparation (however, platelet concentrates may be stored at 22°C either on an agitator or manually mixed once per 24 (48)); the risk of alloimmunization following a first transfusion, leading to ineffective subsequent transfusions and the possibility of adverse reactions (47). Frozen platelet concentrates are an alternative to platelet-rich plasma and are currently available through one animal blood bank (Midwest Animal Blood Services, Stockbridge, Michigan, USA, www.midwestabs.com/VetInfo/platelet_concentrate.htm). Platelet-rich plasma may be more useful in small-sized animals; for larger dogs, it is difficult to obtain a sufficient volume to boost the platelet count effectively. Platelet concentrates, if available, may increase the platelet count more effectively (49). Spontaneous bleeding may occur with platelet counts below $50 \times 10^9/L$ to $75 \times 10^9/L$, but patients with counts as low as $10 \times 10^9/L$ may not show signs of spontaneous bleeding (28). Spontaneous bleeding may also occur with platelet dysfunction at higher platelet counts. In immune-mediated thrombocytopenia, transfused platelets will be rapidly destroyed, the transfusion of several units may be required, and the risk of alloantibody formation is increased (47).

Alternatives to blood products for expansion of plasma volume include different types of colloids, such as dextrans and hetastarch. A drawback of dextrans and hetastarch is that they may alter hemostasis (50,51). A hemoglobin-based oxygen carrier (Oxyglobin; Biopure Corporation, Cambridge, Massachusetts, USA), approved for use in the dog in 1998, is useful in that it can be used as a blood substitute in emergency situations when there is no time to prepare blood products or carry out compatibility testing.

Adverse transfusion reactions

The risk of an adverse reaction is minimized under the following conditions: the administered product has been properly collected, processed, and stored; the donors are healthy animals of known blood group type (dogs that are negative for the DEA-1.1, and DEA-1.2); and proper screening tests have been performed (crossmatching). In veterinary medicine, one study determined that up to 13% of dogs developed an adverse reaction, but all animals survived (52). There are 2 types of adverse reaction, an immediate reaction that occurs during or within 1 to 2 h following transfusion or a delayed reaction that may occur days, months, or years later (53). The severity of an adverse reaction varies from mild (fever) to severe (death).

The most serious transfusion reaction that the practitioner can prevent is an acute hemolytic reaction. This is an immunological reaction that takes place when the patient has circulating natural or acquired antibodies towards donor erythrocytic antigens. Clinical signs are due to the intravascular hemolysis that results in hemoglobinuria, vasoconstriction, renal ischemia, and DIC,

which itself can lead to ischemia in several organ systems and complement activation, resulting in shock. Clinical signs in dogs include fever, tachycardia or bradycardia, hypotension, dyspnea, cyanosis, excessive salivation, tearing, urination, defecation, vomiting, collapse, opisthotonos, cardiac arrest, hemoglobinemia, and hemoglobinuria. The severity of the signs in dogs depends on the volume administered. A clinician presented with an acute hemolytic reaction should interrupt the transfusion immediately and treat for shock, if present. He or she should also verify the blood product being used and retrace the steps that led to the transfusion, including a repetition of the crossmatch procedure (53,54). The acute hemolytic reaction is rare in the dog, due to the low prevalence of naturally occurring anti-erythrocytic antibodies in this species. Non-DEA-7 type dogs may have anti-DEA-7 antibodies, but these antibodies are unlikely to produce a marked hemolytic reaction. The risk is greater in an animal that has previously been transfused, particularly if DEA-1 type blood is administered a second time to a DEA-1-negative dog. In cats, an acute hemolytic reaction is very likely in a type B cat receiving type A blood. The above risks are minimized if DEA-1.1- or DEA-1.2-negative dogs are used and blood is screened for incompatibility, especially in the cat.

Other adverse reactions include nonhemolytic fever in the hour following transfusion; this occurred in approximately 5% of transfusions performed at a veterinary teaching hospital (K.J. Wardrop, unpublished observations). This reaction is most likely associated with circulating antileukocyte antibodies in the recipient. It is important to note that fever may also occur in an acute hemolytic reaction in association with septicemia, if contaminated blood products have been inadvertently administered. Anaphylactic shock (not associated with an acute hemolytic reaction) following transfusions has not been documented in veterinary medicine. Following plasma administration, vomiting or diarrhea may occasionally be observed. Urticaria is not uncommon but seldom poses a danger to the patient and may be treated with antihistamines, with or without glucocorticosteroids. It is probably caused by antibodies against soluble proteins in the blood product administered (plasma). Hypervolemia may result when whole blood is administered to a normovolemic patient; with the rapid administration of a large volume of a blood component; transfusion in cats or small-sized dogs, which, presumably, are more likely to receive an excessive volume of blood; and in patients suffering from cardiovascular, pulmonary, renal, or hepatic compromise. One possible outcome of hypervolemia is pulmonary edema. Clinical signs associated with hypervolemia include cough, tachypnea, dyspnea, or cyanosis. Treatment includes stopping the transfusion, administering diuretics (furosemide) to reduce pulmonary edema, and providing oxygen support (28,54).

Delayed adverse transfusion reactions include delayed hemolytic reaction, transmission of infectious disease, and posttransfusion purpura (55–57). There are possibly lesser known antigens that may provoke antibody production in a patient following transfusion. This may lead to a delayed hemolytic reaction in the days or

weeks following a transfusion or may shorten the half-life of transfused RBCs (19). Clinical signs, if present, vary from fever to icterus. An unexplained drop in packed cell volume may be observed (58) and the Coomb's test may become positive. If a delayed hemolytic reaction is suspected, urine output should be monitored, but treatment is usually unnecessary. Crossmatching prior to transfusion may enable detection of naturally occurring anti-DEA-3, -5, or -7 alloantibodies and prevent an associated delayed transfusion reaction. However, crossmatching will not detect an incompatibility for antigens that trigger sensitization in a recipient, since the antibodies are only produced following transfusion. For this reason, the use of DEA-1.1- and DEA-1.2-negative donor dogs as well as cats of the proper blood type, minimizes the risk of such a reaction. Posttransfusion purpura has been reported in the dog, characterized by the appearance of severe thrombocytopenia in the week following a second transfusion (57). Posttransfusion purpura is caused by the production of antiplatelet antibodies in the patient. Spontaneous remission generally resolves this problem within 1 to 6 wk after the thrombocytopenic episode (59).

In conclusion, the medical decision to transfuse and the product selected depend on several factors. Blood products can be obtained in several ways, depending on the particular requirements of a given practice, either through the purchase of blood products as needed, or through in-house or external donors. The risk of potentially fatal adverse transfusion reactions is higher in cats than in dogs. This risk can be minimized in both species by using known donors and screening assays that permit detection of incompatibility, such as blood typing or crossmatching. These assays are easy to perform either as in-house assays or via a request to an external laboratory.

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